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EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Office Action Summary	Application No.	Applicant(s)	
	10/759,734	GEPSTEIN ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-177, 182-186, 196-199* is/are pending in the application.

4a) Of the above claim(s) *1-175,182-185* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *176,177,186 and 196-199* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment to the claims filed March 5, 2008 has been received and entered. Claims 1-177, 182-186, 196-199 are pending in the application. Applicants have amended claims 176 and 199, while claims 178-181 and 187-195 have been canceled. Claims 176-177, 186, 196-199 are under consideration.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03/05/2008 has been entered.

Election/Restrictions

Applicant's election of claims 176-195 (group IV) in the reply filed on August 17, 2006 was acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Applicants also elected cardiac specific electrical activity for claims 177 and 189 for first action on merit.

Claims 1-175 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on August 17, 2006. It is noted that claims 182-185 were drawn to nonelected subject matter. Therefore, claims 182-185 were also withdrawn because they are drawn to non-elected species.

Claims 176-177, 186, 196-199 drawn to an *in-vitro* culture of isolated human cells that predominantly display at least one characteristic associated with a cardiac phenotype of cardiac specific electrical activity for at least as long as a time period selected from the range of 1-60 days would be examined in the instant application. Claims 176-181, 196-199 are under examination.

Claims 176-177, 186, 196-199 are under consideration.

Withdrawn- Claim Rejections - 35 USC § 112

Claims 176-181, 196-199 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of amendments to the claims.

Withdrawn-Claim Rejections - 35 USC § 102

Claims 176-177, 186, 196-199 rejected under 35 U.S.C. 102(e) as being anticipated by Benvenisty (US Patent 7045353, dated 5/16/2006, effective filing date 8/1/2000) is withdrawn in view of amendments to the claims. However, upon further consideration a new rejection is presented below.

Claims 176-177, 186, 196-199 rejected under 35 U.S.C. 102(a) as being anticipated by Itskovitz-Eldor et al (WO 00/70021, published 11/23/2000) is withdrawn in view of amendments to the claims.

Claims 176-17, 186 and 196-199 are also rejected under 35 U.S.C. 102(b) as being anticipated by Itskovitz-Eldor et al (Mol Med. 2000 Feb; 6(2):88-95, IDS) is withdrawn in view of amendments to the claims.

New-Claim Rejections-Necessitated by amendments - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim interpretation: Clams are directed to an in vitro culture of isolated human embryoid bodies comprising a plurality of non-cystic embryoid bodies each including human cells exhibiting at least one characteristic associated with a cardiac phenotype. In the instant case, the breadth of the claims embrace human EB comprising plurality of non cystic EB containing human cell showing cardiac phenotype. As recited instant in vitro culture comprises a mixed population of embryoid bodies including cystic as well as non cystic human embryoid bodies (hEB).

Claims 176-177, 186, 196-199 are rejected under 35 U.S.C. 102 (e) as being anticipated by Funk et al. (US Patent no 6,667,176, dated 12/23/2003, filed on 10/10/2000, effective filing date 6/22/2000).

Funk et al teach an isolated in vitro suspension culture of human embryoid bodies (EBs) that is transferred onto polyornithine-coated plates for additional 7 days to obtain beating cells exhibiting the cardiomyocyte phenotype as evident from cardiac troponin I staining (see example 5 and figure 6). Furthermore, Funk et al disclose that 8 days after differentiation beating region are identified in all cultures suggesting that hEB contained human cells exhibiting characteristics associated with cardiac phenotype. The cardio specific linage of human cell disclosed by Funk and those embraced by the instant claims appear to be structurally same, therefore,

proliferation potential and other cardiac phenotype including electrical activity of these cells will be inherently present in the cells disclosed by Funk. In the instant case, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, "[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency' under 35 U.S.C. 102, on prima facie obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted]." The burden of proof is similar to that required with respect to product-by-process claims. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)). Further see MPEP § 2113, "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (Citations omitted).

Additionally, "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

Accordingly, Funk et al anticipates claims 176-177, 186, 196-199.

Claims 176-177, 186, 196-199 are rejected under 35 U.S.C. 102 (e) as being anticipated by Thomson et al. (US Patent no: 7,220,584, dated 5/22/2007, filed on 8/1/2003, effective filing date 2/21/2000).

Thomson et al teaches an in vitro culture of human EB containing cells that differentiate to cardiac phenotype (see claims 1-2). Specifically, Thomson et al disclose culture of hEB in suspension for 11 days that are dispensed by mechanical or chemical means and is allowed to reattach to tissue culture plates treated with gelatin or matrix in ES medium (see col. 4, lines 47-52). The resulting hEB culture would inherently contain a mixed population of cystic and non cystic hEB containing human cell having cardiac phenotype particularly since the starting cell and condition for EB formation is similar to one disclosed in the instant application. The cardio specific linage of human cell disclosed by Thomson and those embraced by the instant claims appear to be structurally same, therefore, proliferation potential and other cardiac phenotype of these cells will be inherently present in the cells disclosed by Thomson. Where, in the instant case, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, "[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency' under 35 U.S.C. 102, on prima facie obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted]." The burden of proof is similar to that required with respect to product-by-process claims. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)). Further see MPEP § 2113, "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In

re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (Citations omitted).

Additionally, "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

Accordingly, Thomson et al anticipates claims 176-177, 186, 196-199.

Withdrawn-Claim Rejections - 35 USC § 103

Claims 176-177 and 196-199 rejected under 35 U.S.C. 103(a) as being unpatentable over Itskovitz-Eldor et al (Mol Med. 2000; 6(2):88-95, IDS) and Igelmund et al (Pflugers Arch. 1999 Apr;437(5):669-79) is withdrawn in view of amendments to the claims. However, upon further consideration a new rejection is presented in view of amendments to the claims.

New-Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 176-177, 186, 196-199 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson et al. (US Patent no: 7,220,584, dated 5/22/2007, filed

on 8/1/2003, effective filing date 2/21/2000), Carpenter et al (US Patent application no 20020137204, dated 09/26/2002, filed on 10/23/2001, effective filing date 6/22/2000) and Igelmund et al (Pflugers Arch. 1999 Apr;437(5):669-79, art of record).

Thomson et al teaches an in vitro culture of human EB containing cells that differentiate to cardiac phenotype (see claims 1-2). Specifically, Thomson et al disclose culture of hEB in suspension for 11 days that are dispensed by mechanical or chemical means and is allowed to reattach to tissue culture plates treated with gelatin or matrix in ES medium (see col. 4, lines 47-52). The resulting hEB culture would inherently contain a mixed population of cystic and non cystic hEB containing human cell having cardiac phenotype particularly since the starting cell and condition for EB formation is similar to one disclosed in the instant application.

Prior to instant invention, Carpenter et al disclose transferring human EBs to gelatin-coated plates after 4 days in the suspension cultures. It is noted that EBs attached to the surface after seeding, proliferated and differentiated into different types of cells. Carpenter et al teach spontaneously contracting cells in various regions of the culture after 8 days of differentiation and the number of beating regions increased up to 10^{th}. Carpenter et al disclose that beating cells were morphologically similar to mouse ES cell-derived beating cardiomyocytes known in the art (see para, 262 of the published application).

Although, Thomson/ Carpenter et al taught an in vitro suspension culture of embryoid bodies comprising a heterogeneous mixture of hEB showing cardiac phenotype, however, they differed from claimed invention by not explicitly disclosing further characterization of plurality of EBs.

Prior to instant invention, Igelmund et al (Pflugers Arch. 1999 Apr; 437(5): 669-79) teach a method to investigate the spontaneous electrical activity of cardiomyocyte clusters in EBs, of small groups of cells, and of single cardiomyocytes (see page 670, col. 1, lines 2-4). Igelmund et al disclose that single embryoid bodies

are plated for multiple recording from several locations of individual EBs (Figure 1). The electrode matrix consisted of 60 TiN-coated gold electrodes with a diameter of 10 or 30 µm, arranged in eight columns and eight rows with a distance of 100 or 200 µm between adjacent electrodes (see Figs. 4, 5) (see page 670, column 1, extracellular recording section). Igelmund et al teach that by recording population action potentials from the beating areas of EB, one could determine the electrical interaction between cardiomyocytes and beating activity (see page 677, paragraph 2). Igelmund et al conclude that this method of field potential recordings from clusters of ES cell-derived cardiomyocytes within EBs provide a useful tool for studying in vitro chronotropy and action potential propagation (see page 678, column 1, paragraph 2). However, Igelmund et al do not explicitly teach recording action potential of human cells.

Accordingly, in view of the teachings of Thomson, Carpenter and Igelmund, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to further characterize the human EBs containing human cells exhibiting cardiac phenotype taught by Thomson or Carpenter using the method disclosed by Igelmund et al by substituting the mouse EB with functionally equivalent human EB disclosed by Thomson or Carpenter in order to determine the electrical interaction between cardiomyocytes and beating activity of human cardiomyocytes. Igelmund had already taught a method to use multiple recording from several locations of individual EBs using electrode matrix to determine the action potential from the beating areas (*supra*). In addition, at the time of filing of this application cardiomyocytes differentiated from embryonic stem cell of different species were also known in the art as taught by Thomson, Carpenter and discussed above. It would have been prima facie obvious for one of ordinary skill in the art to replace the mouse EB with human EB as action potential recordings from clusters of ES cell-derived cardiomyocytes within EBs would have provided in vitro chronotropy and action potential propagation of these cells for their potential use in

transplantation medicine. One who would practiced the invention would have had reasonable expectation of success because Igelmund et al had already taught the method of extracellular recordings of the population action potentials of cardiomyocyte clusters to perform long-term recordings (for up to several weeks) from individual EBs under cell culture conditions. Thomson, Carpenter taught human EB containing cardiac linage cells showing cardiac phenotype. Igelmund et al had had already described the use of multiple electrode array system to map the beating area of EBs with electrical activity. Thus, it would have only required routine experimentation to substitute the mouse cell with human cardiomyocytes obtained from human cell to determine the action potential of pulsating cardiomyocytes.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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